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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,803	06/30/2006	Huafang Gao	514572001200	5370
25225 7590 05/27/2009 MORRISON & FOERSTER LLP 12531 HIGH BLUFF DRIVE SUITE 100 SAN DIEGO, CA 92130-2040			EXAMINER BHAT, NARAYAN KAMESHWAR	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/562,803

**Applicant(s)**

GAO ET AL.

**Examiner**

NARAYAN K. BHAT

**Art Unit**

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 10 February 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-846)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2008 has been entered.

***Status of the Claims***

2. This action is in response to papers filed on October 30, 2008 and February 10, 2009.
3. Claims 1, 7, 9, 22, 24, 41, 43 and 58 were amended, claims 2, 3, 61 and 65-76 were cancelled and new claims 77 and 78 were added on October 30, 2008.
4. Claim amendments filed October 30, 2008 necessitated further lack of unity requirement to select a single probe or combination of probes from SEQ ID NOS listed in Table 1.
5. In response to further lack of unity requirement, Applicants elected with traverse combination of all the probes listed in Table 1 consisting of ***SEQ ID NO 1-214***, further amended claim 1 and added new claims 79 and 80 in the papers filed on February 10, 2009.
6. The previous rejections under 35 USC § 102 (b) and 103 (a) not reiterated below have been withdrawn in view of claim amendments. Applicant's arguments filed on

October 30, 2008 and February 10, 2009 have been fully considered and addressed following rejections.

7. Claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 are pending in this application and are under prosecution.

***Response to Further Lack of Unity Requirement***

8. Applicants traverse the species election on the grounds that limiting the claims to only some HLA probes effectively eviscerates the scope of the subject matter and there is no additional search burden (Remarks, Feb. 10, 2009). This argument is not persuasive because each of the nucleotide probes listed in Table 1 is a unique molecule because it detects different type of HLA genotypes, i.e., complementary to different HLA target nucleotide sequence. Therefore there is no special feature that joins the differently claimed probes listed in Table 1. Since there is a lack of unity between probes listed in Table 1, the burden of the search of these different inventions is moot.

***Amendments to Claims***

9. Amendments to the claim 1 have been reviewed and entered.

***Claim Rejections - 35 USC § 112-First Paragraph***

***New Matter***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)".

The new limitation of "replacing 'B' with nucleotide 'G' in SEQ ID NO 13" in claim 1 appears to represent new matter. The SEQ ID NO 213 contains 'B' in the specification as originally filed. The letter "B" as an IUPAC symbol refers to 5-bromouridine (<http://www.chem.qmul.ac.uk/iupac/misc/naabb.html>). By replacing 5-bromouridine with Guanosine in the nucleotide sequence broadens the scope of the invention and therefore appears to represent a new matter. No specific basis for this limitation was identified in the specification, nor did a review of the specification by the examiner find any basis for the limitation. Since no basis has been identified, the claims are rejected as incorporating new matter. Since claims 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 are dependent from claim 1 they are also rejected as incorporating a new matter.

**35 USC § 112 –Second paragraph**

12. Previous rejections of claims 1-4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53 and 57-61 are withdrawn in view of claim amendments or cancellation of said claims.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 4, 9, 22, 24, 26, 28, 30-31, 37, 43, 46, 49, 53, 57-60 and 77-79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Petersdorf et al (WO 00/79006 published Dec. 28,

2000), Samartziduo et al (Life science news, 2001, 8, 1-3) in view of Trau et al (Anal. Chem. 2002, 74, 3168-3173).

Regarding claim 1, Apple et al teaches a method for typing a target HLA gene as discussed below.

Regarding step 'a', Apple et al teaches isolating the target nucleic acids from cells comprising a target HLA nucleotide sequences that is at least a part of the HLA gene and optionally lines another nucleotide sequence not related to target HLA gene (Example 7, column 41, lines 23-27).

Regarding step 'b', Apple et al a reverse dot blot, (i.e., a chip) comprising a membrane support suitable for use in nucleic acid hybridization having immobilized thereon an oligonucleotide probe complementary to DRB target nucleotide sequence (Example 8, column 43, lines 35-60).

Regarding step 'b'(i), Apple et al teaches probe sequence hybridizes under high stringency (Table 4, column 28, lines 1-2).

Regarding step 'b'(ii), Apple et al teaches nucleotide probe sequence comprises at least 90% identity to nucleotide sequence SEQ ID NO182, 193-196 and 198-202 as evidenced by blast analysis of the SEQ ID NO 7 of Apple et al (See the blast analysis brochure).

Apple et al do not teach chip comprising a combination of probes consisting of SEQID NOS 1-214.

Apple et al further teaches that the chip contains probes specific for particular allele type and additionally contains a control probe that detects all of the alleles

(column 53, lines 50-67, column 54, lines 15-30 and column 56, lines 33-41). The control probe of Apple et al is the positive control probe as defined in the instant specification (instant specification, USPGPUB, paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Apple et al also teaches that positive control probe create a hybridization signal having intensity equal or less than the positive dots on the chip and provides a guide as to the minimum dot intensity that should be scored as a positive (column 56, lines 36-41).

Apple et al do not teach a negative control probe, hybridization control probe and an immobilization control probe.

Regarding step 'c', Apple et al teaches hybridizing the sample obtained in step 'a' with the chip obtained in step 'b' and assessing hybridization between said target HLA nucleotide sequence and/or said another nucleotide sequence and said probes comprised on said chip to determine the type of HLA target gene (Figs 10-13, column 56, lines 42-48).

Regarding claim 4, Apple et al teaches that the suitable sample is a human bladder tissue that comprises human nucleic acid (column 42, lines 46-54).

Regarding claim 9, Apple et al teaches that the preparation of the target nucleotide sequence comprises a nucleic acid amplification step (column 3, lines 62-65).

Regarding claim 22, Apple et al teaches that the target nucleotide sequence is amplified by PCR using biotinylated primer for hybridization and detection by SA-HRP

(column 43, lines 40-48) thus teaching DNA is single stranded at the time of hybridization.

Regarding claim 24, Apple et al teaches that a labeled biotinylated target nucleotide sequence is obtained (column 43, lines 40-48).

Regarding claim 26, Apple et al teaches probe DRB 46 complementary to the DR 11 positive control probe (column 53, lines 50-67).

Regarding claim 28, Apple et al teaches that the probes are tiled with poly dT to attach the probe to the membrane, thus teaching probe comprised on the chip are modified (column 43, lines 54-60).

Regarding claim 30, Apple et al teaches 22 different DRB probes fixed on the membrane, i.e., chip that meets the limitation of the chip comprises 1-400 different types of probes (Examples 8 and 9, columns 53 and 54 and lines 50-67 and 15-38).

Regarding claim 31, Apple et al teaches two panels of probes containing 11 different DRB probes fixed on the membrane, i.e., chip and further teaches one panel for hybridizing with the DRB amplification products (Example 9, column 53, lines 51-67) and the other with the DRB1-specific amplification products (Example 9, column 54, lines 15-38) thus teaching multiple arrays of probes and each array comprises 11 probes that meets the limitation of each array comprises 1-400 different types of probes.

Regarding claim 37, Apple et al teaches that 5 to 10 picomoles of the probes, i.e., multiple copies of a probe is immobilized on the chip (column 44, lines 31-35).

Regarding claim 43, Apple et al do not teach hybridization control probe is complementary to a synthetic nucleotide sequence not related to a target gene.

Regarding claim 46, Apple et al do not teach immobilization control probe.

Regarding claim 49, Apple et al teaches hybridization solution comprises SSPE and SDS, i.e., surfactant (column 44, lines 52-55).

Regarding claim 53, Apple et al teaches that the hybridization reaction is conducted at a temperature of 50 C which is about 42.C to about 70C (column 44, line 52).

Regarding claims 57-60, Apple et al do not teach immobilization efficiency, hybridization efficiency assessed by labeled synthetic nucleotide sequence not related to the target HLA gene.

As described above, regarding step 'b' (i) and (ii), Apple et al do not teach chip comprising a combination of probes consisting of SEQIDNOS 1-214. It is noted that the SEQID NO 1-214 probes are derived against HLA-A, B and DRB1 locus. As described above, Apple et al teaches probes for genotyping for DRB locus (Abstract). Probes for HLA-A and B loci were known in the art at the time of the claimed invention was made as taught by Petersdorf et al.

Petersdorf et al teaches a method for HLA typing of both class I and II alleles (pg. 5, lines 25-31) comprising oligonucleotide arrays for high resolution HLA typing comprising probes representing 98% of the known polymorphisms of the HLA class 1 locus (pg. 4, lines 7-16). Petersdorf et al also teaches that the probes have at least 90% identity with HLA Class I target gene (Table 2) and further teaches array comprises at least 137 different oligonucleotide probes for HLA (Table 2). Petersdorf et al also

teaches that the array comprises at least 3,000 different oligonucleotide probes (pg. 34, lines 25-27).

Regarding claims 77-79, Apple et al teaches that the chip comprises nucleotide sequence for an HAL-DRB (Example 9). Petersdorf et al teaches that the chip comprises an HLA A and HLAB nucleotide probe (Table 1 and 2).

Thus combined teachings of Apple et al and Petersdorf et al provide a chip comprising probes for HLA-A, HLA-A, B and DRB loci up to 98% of the known polymorphism. The claimed SEQ ID NOS 1-214 are obvious over the cited prior art, absent secondary considerations.

Petersdorf et al further teaches that HLA arrays provide tools for determining the donor/recipient compatibility in tissue transplantation (pg. 29, lines 5-7).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the HLA DRbeta probe chip of Apple et al with probes for HLA-a and B loci of Petersdorf et al with a reasonable expectation of success.

An artisan would be motivated to modify the HLA DRbeta probe chip of Apple et al with the expected benefit of having a chip comprising probes of HLA-A, B and DRB loci for determining the donor/recipient compatibility in tissue transplantation as taught by Petersdorf et al (pg. 29, lines 5-7).

Apple et al and Petersdorf et al teach positive control probe and reference sequence probe (Petersdorf et al, pg. 14, line 1) but do not teach a negative control

probe, a hybridization control probe and a synthetic probe complementary to hybridization control probe. However, different control probes were known in the art before the invention was made as taught by Samartziduo et al, who teaches microarray scorecard controls on the chip that includes positive, negative hybridization control probes and probes for dynamic range and ratio controls (Fig. 1, # 2, pg. 1, column 2, paragraph 3).

Regarding claim 43, Samartziduo et al teaches that the hybridization control probe is complementary to a synthetic YIR nucleotides not related to the target HLA gene (Fig. 1, # 2, pg. 1, column 2, paragraph 3).

Samartziduo et al further teaches that hybridization controls make a powerful tool for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio (pg. 2, column 1, paragraph 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the control probes of Apple et al with negative control, hybridization control and synthetic control probe of Samartziduo et al with a reasonable expectation of success.

An artisan would be motivated to modify the control probes of Apple et al with the expected benefit of using a better controls for validation of microarray experiments, allowing assessment of target attachment, hybridization uniformity, detection limits, dynamic range and expression ratio as taught by Samartziduo et al (pg. 2, column 1, paragraph 1).

Apple et al, Petersdorf et al and Samartziduo et al do not teach an immobilization control probe to assess immobilization efficiency. However, an immobilization control probe was known in the art at the time of the invention was made as taught by Trau et al, who teaches an immobilization control probe on the chip (pg. 3169, column 2, paragraph 3, Table 1, Fig. 4 A-D, lane 7).

Regarding claims 57-60, Trau et al teaches an array of closely related genes from medicinal plants (pg. 3170, column 2, paragraph 2) and teaches explicitly probes for five different genes (PP, DI, AM, TG and HF) and an immobilization control (Fig. 4, Table 1, limitation of claim 57). Since there is no limiting definition for synthetic nucleotide sequence, the immobilization control probe, which is labeled, is the synthetic nucleotide probe (Trau et al, Table 1) and the probe for PP gene is the hybridization control probe. Trau et al also teaches the analysis of the hybridization of the immobilization control probe and the PP probe (Fig. 4A, limitation of claim 58) thus providing the assessment of hybridization efficiency between hybridization control probe and the synthetic nucleotide.

Trau et al further teaches the hybridization of PP sample to PP probe (Fig. 4A, column 2) and AM probe (Fig. 4A, column 3), which is a negative control probe, and meets the requirement as defined in the instant specification (paragraph 0027) because it comprises multiple base pair changes compared to PP probe (Table 1). Trau et al teaches the ratio of hybridization signal (specific hybridization, Fig. 4A, column 2) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 compared to the ratio of hybridization signal (specific hybridization) to noise (unspecific

hybridization with AM probe in Fig. 4A, column 3) is greater than 80 (pg, 3172, column 1, paragraph 1) thus teaching the increased ratio between the hybridization signal involving the positive hybridization control probe and the hybridization signal involving the negative hybridization control probe (limitation of claim 59).

Trau et al also teaches an embodiment, wherein the ratio of hybridization signal (specific hybridization, Fig. 4B, column 6) to noise (background, Fig. 4A, columns 1 and 8 no probes) is greater than 150 (pg, 3172, column 1, paragraph 1, limitation of claim 60, step 'a') and further teaches the signal to noise ratio range from 150 to 4 (Fig. 4C, column 6) to 2 (Fig. 4D, column 6) thus teaching a range of the ratio of hybridization signal (pg, 3172, column 1, paragraph 1, limitation of claim 60, step 'b') and further teaches comparing the hybridization signal of all probes giving positive signals (Fig. 4A, limitation of claim 60, step 'c') and two positive signals (probe PP and DI) of closely related genes (Fig. 4 A and B, limitation of claim 60, step 'd'). Trau et al also teaches further improvement in quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the control probes and data analysis of Apple et al, Petersdorf et al and Samartziduo et al with immobilization and synthetic control probes of Trau et al with a reasonable expectation of success.

An artisan would be motivated to modify the control probes and data analysis of Apple et al with the expected benefit of improving quantifying microarray data at a signal to noise ratio of 2, by adjusting template concentration for hybridization and normalizing hybridization data for each spot on the chip in relation to the amount of immobilized probe thereby reducing the spot-to-spot variation due to unequal immobilization as taught by Trau et al (Fig. 5, pgs. 3172 and 3173, column 1, paragraph 1).

16. Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Petersdorf et al (WO 00/79006 published Dec. 28, 2000), Samartzidou et al (Life science news, 2001, 8, 1-3) and Trau et al (Anal. Chem. 2002, 74, 3168-3173) as applied to claim 1 as above and further in view of Patterson et al (USPN 5,843,640 issued Dec. 1998).

Claim 7 is dependent from claim 1. Teachings of Apple et al, Petersdorf et al Samartzidou et al and Trau et al regarding claim 1 are described above in section 15.

Regarding claim 7, Apple et al teaches target nucleic acids are obtained from human bladder tissues and cell lines (Example 7, columns 41 and 42, lines 22-30 and 46-54). Apple et al, Petersdorf et al, Samartzidou et al and Trau et al do not teach about isolating target leukocyte cell using magnetic micro bead. However, method of using magnetic micro bead to isolate the leukocytes was known in the art at the time of the invention was made as taught by Patterson et al, who teaches the isolation of lymphocytes from PBMCs using magnetic beads and further teaches that the magnetic

bead method provides highly enriched population of CD4 lymphocytes, i. e., leukocytes (column 12, lines 46-50).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the target cell isolation method of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al with the magnetic bead method of Patterson et al with a reasonable expectation of success.

An artisan would have motivated to modify the target cell isolation method of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al with the expected benefit of obtaining highly enriched population of leukocytes from PBMCs as taught by Patterson et al (column 12, lines 46-50).

17. Claims 1 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Petersdorf et al (WO 00/79006 published Dec. 28, 2000), Samartzidou et al (Life science news, 2001, 8, 1-3) and Trau et al (Anal. Chem. 2002, 74, 3168-3173) as applied to claim 1 as above and further in view of Straus (USPGPUB NO. 2002/0086289 published July 4, 2002).

Claim 41 is dependent from claim 1. Teachings of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al regarding claim 1 are described previously in this office action in section 15.

Regarding claim 41, Apple et al, Petersdorf et al, Samartzidou et al and Trau et al teaches a control probe that detects all of the HLA alleles (columns 53, lines 50-67).

The control probe of Apple et al is the positive control probe as defined in the instant specification (paragraph 0027) and also because it detects all of the DRB alleles (column 56, lines 33-41). Apple et al, Samartzidou et al, Trau et al and Stockton are silent about positive control probe complementarity to a portion of the target nucleotide sequence. However, positive control probe complementary to a portion of the target nucleotide sequence was known in the art at the time of the invention was made as taught by Straus, who teaches a method for genomic profiling, which includes a positive control probe on the chip hybridizes to a target control sequence (paragraphs 191 and 210), which meets the definition of the positive control probe as defined in the instant specification (paragraph 0027). Straus also teaches adding positive control DNA sample to the experimental DNA sample for amplification thus teaching nucleotide sequence amplified synchronically with the experimental sample and further teaches that positive control probes are detected in all assays except for failure of assay steps (paragraph 0210). Straus further teaches failure to detect a signal from positive control probe indicates a false negative result (paragraph 0210).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the positive control probe of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al with the positive control probe complementary to a portion of target sequence of Straus with a reasonable expectation of success.

An artisan would be motivated modify the positive control probe of Apple et al, Petersdorf et al, Samartzidou et al and Trau et with the expected benefit of confirming

the false negative result due to failure to detect a signal from positive control probe as taught by Straus (paragraph 0210).

18. Claims 1 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Petersdorf et al (WO 00/79006 published Dec. 28, 2000), Samartziduo et al (Life science news, 2001, 8, 1-3) and Trau et al (Anal. Chem. 2002, 74, 3168-3173) and Straus (USPGPUB NO. 2002/0086289 published July 4, 2002) and further in view of Delenstarr et al (USPGPUBNO. 2002/0051973 published May 2, 2002).

Claim 42 is dependent from claim 41, which is dependent from claim 1. Teachings of Apple et al, Petersdorf et al, Samartzidou et al, Trau et al and Straus regarding claims 1 and 41 are described previously in this office action in 17.

Regarding claim 42, Straus teaches a negative control probe (paragraph 180) but do not teach negative control probe has about 1-3 base pair mismatches compared to positive control probe. However, negative control probe having about 1-3 base pair mismatches compared to positive control probe was in the art at the time of the invention was made as taught by Delenstarr, who teaches a positive control probe (paragraph 0076) and a negative control probe (paragraph 0075). Delenstarr also teaches that negative control probe (paragraphs 151-152, Table 5, SEQ ID NO. 32) has about 3 base pair mismatches when compared to the positive control probe (paragraph 0129, SEQ ID NO. 2). Delenstarr also teaches a method to identify the shortest length of background probes, i.e., negative control probe (Delenstarr et al also refers negative

control probe as background probes, paragraph 0075) that mimics the properties of longer probes, yet have reduced affinities for complementary target sequence (paragraph 150).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the negative control probe of Apple et al, Petersdorf et al, Samartzidou et al, Trau et al and Straus for the genomic profiling with shorter negative control probe of Delenstarr et al with a reasonable expectation of success.

An artisan would be motivated modify the negative control probe of Apple et al, Petersdorf et al, Samartzidou et al, Trau et al and Straus with the expected benefit of using a negative control probe of shorter length that mimics longer probe properties, yet having reduced affinity complementary target sequence as taught by Delenstarr et al (paragraph 150).

19. Claims 1 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable Apple et al (USPN 5,567,809 issued Oct. 22, 1996), Petersdorf et al (WO 00/79006 published Dec. 28, 2000), Samartzidou et al (Life science news, 2001, 8, 1-3) and Trau et al (Anal. Chem. 2002, 74, 3168-3173) as applied to claim 1 as above in view of Stockton et al (USPGPUB NO. 2002/01875505 published Dec. 12, 2002).

Claim 80 is dependent from claim 1. Teachings of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al regarding claim 1 are described above in section 15.

As described above, Apple et al and Samartzidou et al teaches positive control probes. Apple et al, Petersdorf et al, Samartzidou et al and Trau et al do not teach about multiple positive control probes with length and sequence variations. However, multiple positive control probes with length and sequence variations were known in the art at the time of the claimed invention was made as taught by Stockton, who teaches genotyping method comprising a plurality of positive control oligonucleotides to which the nucleic acid of interest hybridizes and a plurality of negative control oligonucleotides to which nucleic acid of interest do not hybridize (paragraphs 0043 and 0044).

Stockton also teaches that positive control oligonucleotides further comprise a first positive control oligonucleotide containing first boundary sequence without nucleic acid marker and without second boundary sequence, a second positive control oligonucleotide containing second boundary sequence without nucleic acid marker and without first boundary sequence, the third positive control oligonucleotide containing the first boundary sequence and N+A repeats of the nucleic acid element without the second boundary sequence (paragraph 0045). Stockton further teaches nucleic acid repeat elements are short repeat sequences comprising 2 to 10bases in length (paragraphs 0017-0018). Stockton also teaches that positive control oligonucleotide further comprises an oligonucleotide containing just the nucleic acid marker (e.g., repeats of the nucleic acid sequence elements, paragraph 0043). Teachings of Stockton thus provide multiple positive control probes on the chip having variations in length and sequences as claimed.

Stockton also teaches the positive control oligonucleotide containing the nucleic acid marker without a first or a second boundary sequences always gives the positive signal (paragraph 0043). Stockton further teaches that positive control oligonucleotides containing N+A repeats less than nucleic acid to be detected gives negative signal (paragraph 0043). Combined teachings of Stockton of positive and negative signal from the positive control oligonucleotides meet the limitation of creating a group of hybridization signals having strong to weak orderly magnitude.

Stockton teaches that arrays containing multiple positive control oligonucleotides with variations in length and sequences are very useful in identifying micro deletions, short sequence repeat polymorphism, SNP, allele specific polymorphism and variable tandem repeat polymorphisms and detection of mutations associated with cystic fibrosis (paragraphs 0014 and 0062-0063).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the positive control probe of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al with multiple positive control with variations in length and sequences of Stockton with a reasonable expectation of success.

An artisan would be motivated to modify the positive control probe of Apple et al, Petersdorf et al, Samartzidou et al and Trau et al with the expected benefit of having multiple positive control oligonucleotides with variations in length and sequences, which are very useful in identifying micro deletions, short sequence repeat polymorphism, SNP, allele specific polymorphism and variable tandem repeat polymorphisms and

detection of mutations associated with cystic fibrosis as taught by Stockton (paragraphs 0014 and 0062-000063).

### **Response to remarks from the Applicants**

#### ***Rejections under 35 U.S.C. § 103(a)***

20. Applicant's arguments filed on October 30, 2008 with respect to claims 1, 3-4, 9, 22, 24, 26, 28, 30-31, 37, 43, 46, 49, 53 and 57-61 as being unpatentable over Apple et al, Samartzidou et al, Trau et al and Stockton et al have been fully considered but are moot in view of withdrawn rejections and new grounds of rejection set forth in this office action necessitated by the claim amendments (Remarks, pgs. 7-9).

Applicant's arguments with respect to rejection of dependent claims over combination of references are also moot view of withdrawn rejections and new grounds of rejection set forth in this office action necessitated by the claim amendments (Remarks, pg. 8).

Applicants further argue that Apple et al do not teach a negative control probe, a hybridization control probe, an immobilization control probe, or multiple positive control probes with variations in length and sequence (Remarks, pg. 9, paragraph 1). This argument is not persuasive because as described above in section 15, Samartzidou et al teaches a negative control probe, a hybridization control probe. Trau et al teaches an immobilization control probe. Stockton et al teaches multiple positive control probes with variations in length and sequence.

Claim 1 as amended requires the chip consist of probes SEQIDNOS 1-214. However, it is noted that probes are derived against HLA-A, HLA-B and HLA-DRB loci. As described above in section 8, Apple et al and Petersdorf et al teach probes derived against said 3 loci. Probes taught by Apple et al comprise multiple SEQIDNOS from Table 1. Therefore the claimed SEQ ID NOS 1-214 are obvious over the cited prior art, absent secondary considerations. Further more, as described above, Apple et al, Petersdorf et al, Samartzidou et al, Trau et al and Stockton et al teach different control probes as recited in claim 1. It is maintained that Apple et al, Petersdorf et al, Samartzidou et al and Trau et al teach the steps as recited in claim 1. Therefore, arguments are not persuasive.

### ***Conclusion***

21. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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